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Cancer Immunotherapy with BCG for Patients with Stomach Cancers

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Introdution

It has long been said that BCG (Bacillus Calmette and Guérin) is a potent non-specific stimulator of the reticuloendothelial system[3]. Some investigators have more recently found that BCG has prominent preventive effect against some bacterial or viral infections other than tuberculosis. Recently, it has been found that BCG is a representative agent causing a delayed cutaneous hypersensitivity reaction in which T-cells and macrophages participate.

Since the second half of the 1960's, Morton[2] and Mathé[1] have reported that immunotherapy with BCG was effective in prolonging remissions in malignant melanoma and leukemia. We welcomed their reports because we have long waited for clinical application of BCG as a supplemental cancer therapeutic agent. Unfortunately, there has been no available information concerning BCG immunotherapy for patients with cancers of the gastrointestinal tract in Japan. Since Spark's[4] report in 1973, cancer non-specific immunotherapy with BCG (CNIc̄BCG) has been used to treat patients with stomach cancers after palliative or non-curative surgery. Some investigators insist that BCG is not effective in controlling cancers of the gastrointestinal tract, such as stomach and colon. We have, however, noted the interesting result that the patients who received CNIc̄BCG survived longer than untreated controls.

Methods and Materials

Procedures of cancer non-specieic immunotherapy (CNI)

BCG was administered by a multiple puncture tine technique. A freeze-dried strain obtained from the Japan BCG manufacturing company was used. Both upper arms and groins were sterilized. A five by five centimeter square was marked at each area. A fresh suspension equivalent to ten mg of BCG was applied to make a wet film in each square, followed by sixteen punctures with a nine-tine vaccinating disk. BCG was given every two

Key Words : BCG, CNIBc̄CG, Cellular immune defense system, T-cells, Immunoglobulins.

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weeks. Ten BCG inoculations made one course of immunotherapy. The delayed cutaneous hypersensitivity reaction was read in two weeks and was classified into six grades; negative to four plus positive, as shown in Figs. 1 to 5. The new simplified classification was adopted practically for evaluation of the effectiveness of BCG immunotherapy as well as the ability of patients to develop an immune response since the original six-graded classification was slightly complicated to handle statistically. Negative to one plus positive is expressed as negative, and two to four plus positive as positive. Thus patients receiving CNIcBCG were

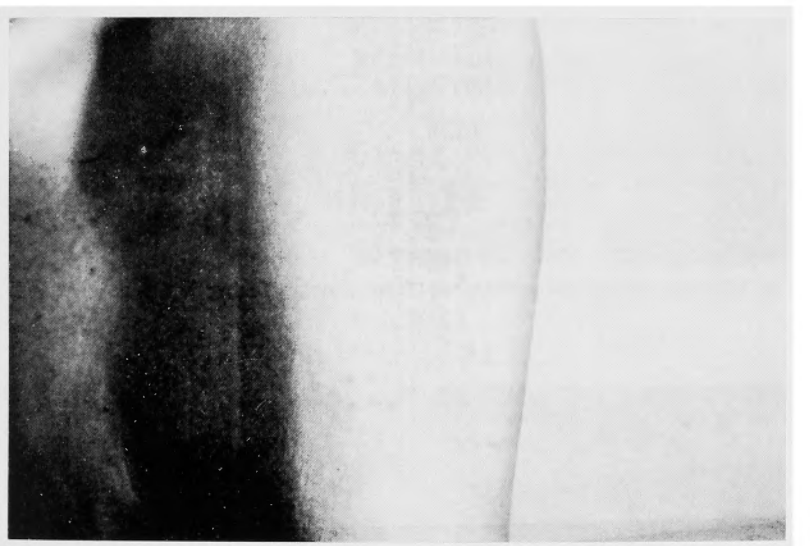

Fig. 1. plus-minus or one-plus positve reaction; scattered red spots and few vesicles with redness.

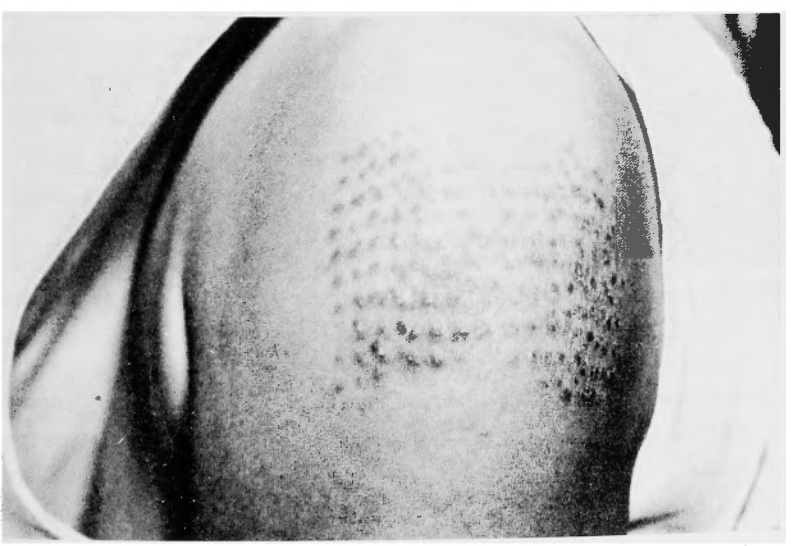

Fig. 2. two-plus posive reaction ; red vesicles appearing in the whole square inoculated with BCG.

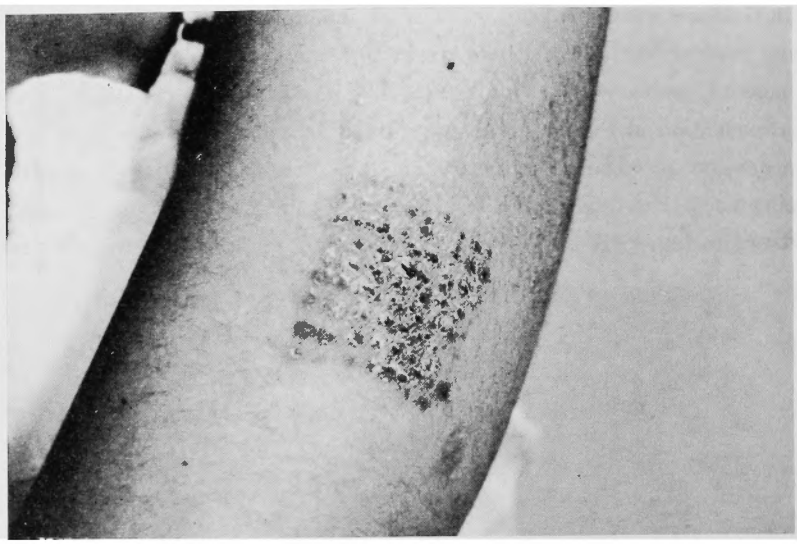

Fig. 3. three-plus positive reaction ; red vesicles fusing with one another.

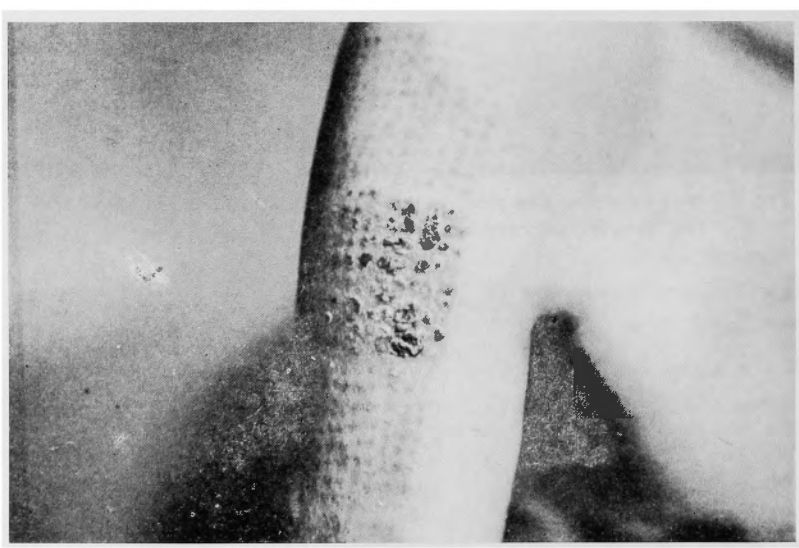

Fig. 4. four-plus positive reaction ; the strongest reaction with formation of ulcers or scabs.

divided into two groups in relation to delayed cutaneous hypersensitivity reaction to BCG ; one negative and the other positive. There are four subgroups ; 1) true negative, 2) false negative showing a negative reaction in the beginning but becoming positive later, 3) false positive showing positive reactions at first, followed by negative ones subsequently, and 4) true positive showing positive reactions throughout the whole course of immunotherapy. True negative and false positive are expressed as negative, and false negative and

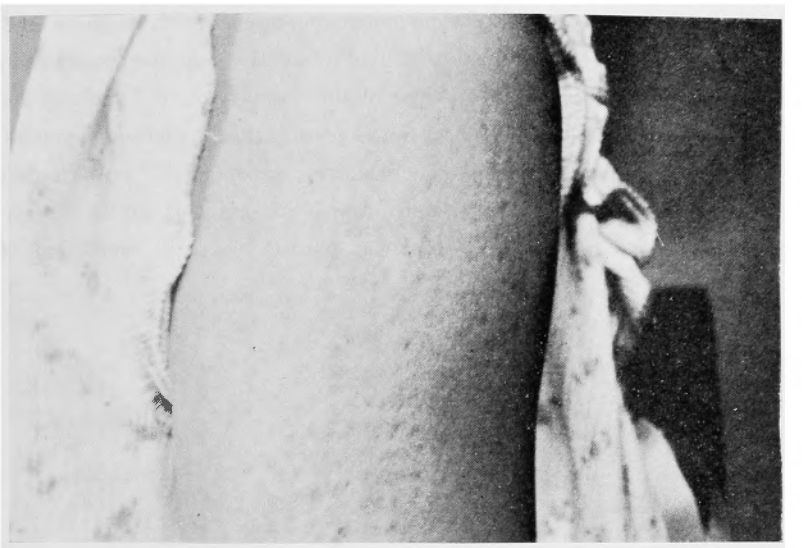

Fig. 5. skin two months after the termination of BCG inoculation ; negligible multiple tiny scars.

true positive as positive. The strongest skin reaction recorded throughout CNIcBCG was used for the present study.

Skin tests for immunocompetency, routine laboratory exams and others necessary for CNIcBCG

PPD of tuberculin was used mainly to check immunocompetency of patients with stomach cancers before CNIcBCG. Even if the skin reaction was negative, the patients received immunotherapy. Determination of immunoglobulins, IgA, IgG, IgM, electrophoresis, alkaline phosphatase, GPT, LDH, CRP, hematology, and urinalysis was performed once or twice before and once a month during and after CNI. If the patient's condition was good, T-cells were determined once or twice before and once a month during CNI. A chest X-ray was taken to eliminate patients with active tuberculosis before CNI. GIS was performed at regular intervals before, during, and after CNI.

Patients

The patients receiving CNI were all over twenty years old and had been treated with relative curative or non-curative surgery. The diagnosis was confirmed pathohistologically as cancer. The stage was determined according to the general rules for the gastric cancer study in surgery and pathology issued by the Japanese Research Society for Gastric Cancer. Most of the patients received CNIcBCG two to four weeks after surgery.

Results

From December, 1973 to December, 1975, twenty-five postoperative patients with stomach cancer received CNIcBCG at the Japan Baptist Hospital. It is noteworthy that there was

a difference in the postoperative survival time between patients with negative and positive skin reaction to BCG. Three of the twenty-five had a negative reaction twenty-two a positive reaction. The mean postoperative survival time of the former was 6.7 months and that of the latter was 16.8 months, as shown in Fig. 6, suggesting that the cellular immune response was retained in patients with advanced stomach cancer, except those in the terminal stage. We were surprised to find that there was a difference in one-year survival rates between group (A) patients who received CNIcBCG and the control group (B) consisting of patients

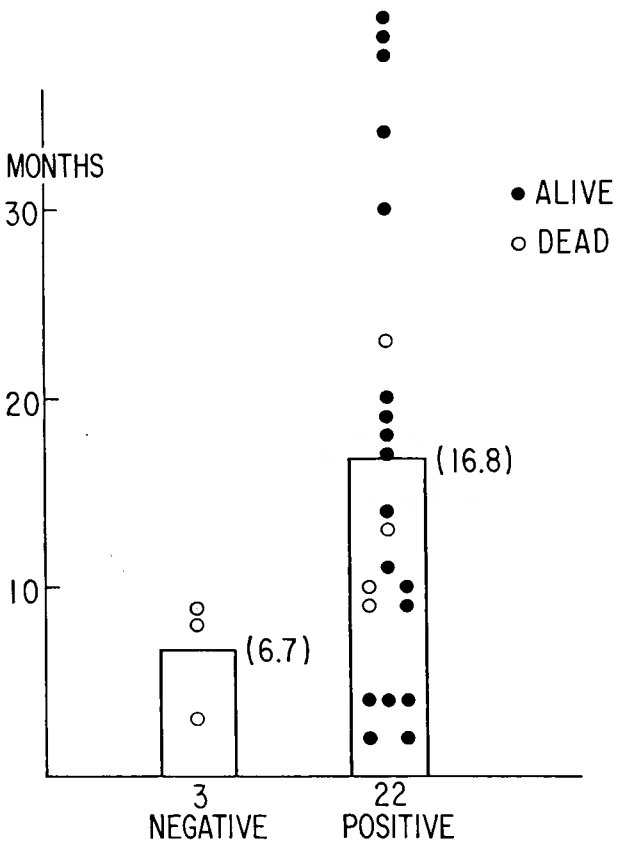

Fig. 6. difference in the postoperative survival time between patients with negative and positive skin reactions to BCG.

treated by surgery for stomach cancer from 1965 to 1970. The postoperative one-year survival of eleven patients receiving CNIcBCG during 1974 was 100% and that of the controls was 53.1%, as shown in Fig. 7, suggesting that the clinical use of BCG immunotherapy is effective as supplemental cancer therapy, even though improvement in surgical procedures and in chemotherapy might have a more potent influence on the difference between the two groups.

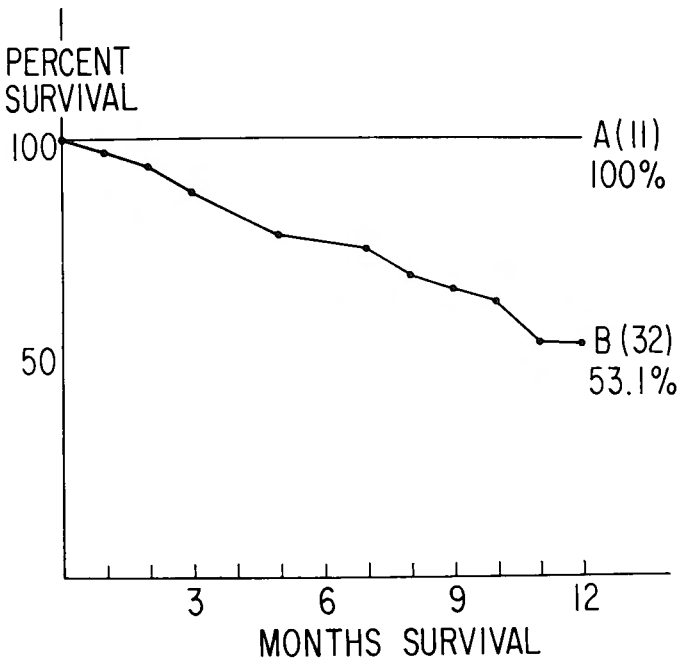

Fig. 7. difference in one-year survival rates between the patient group (A) which received CNIcBCG and the control group (B) ; ages ranged from 26 to 78 and stage II to IV.

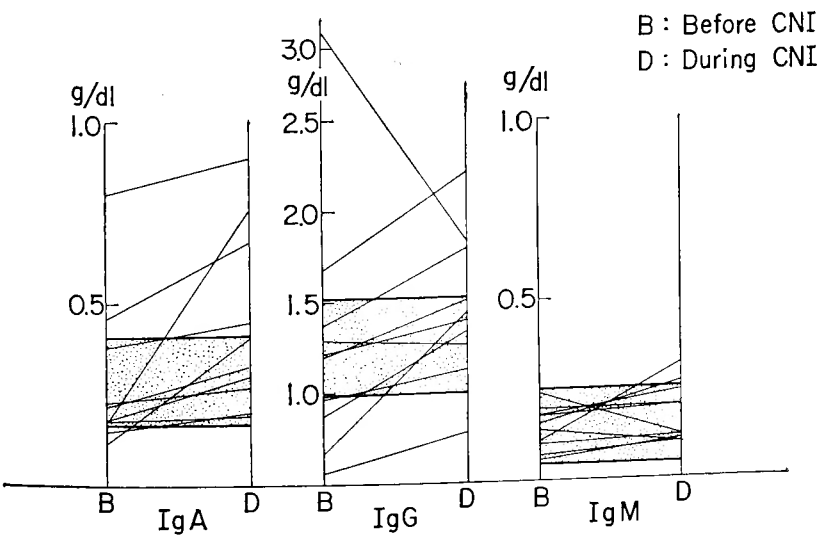

Fig. 8. changes of IgA, IgG and IgM in ten patients before and during CNIcBCG.

Changes of IgA, IgG and IgM in ten patients before and during CNI are shown in Fig. 8. IgA increased in all ten; in the two cases in which it increased above the normal maximum range death occurred. IgG increased in two patients above the normal maximum level after CNI ; they also died. IgM did not show any remarkable change in relation to CNI. Changes in total serum protein, albumin, α_1-, α_2-, β-, and γ-globulin in individual patients before and during CNI are demonstrated in Fig. 9. Total serum protein showed

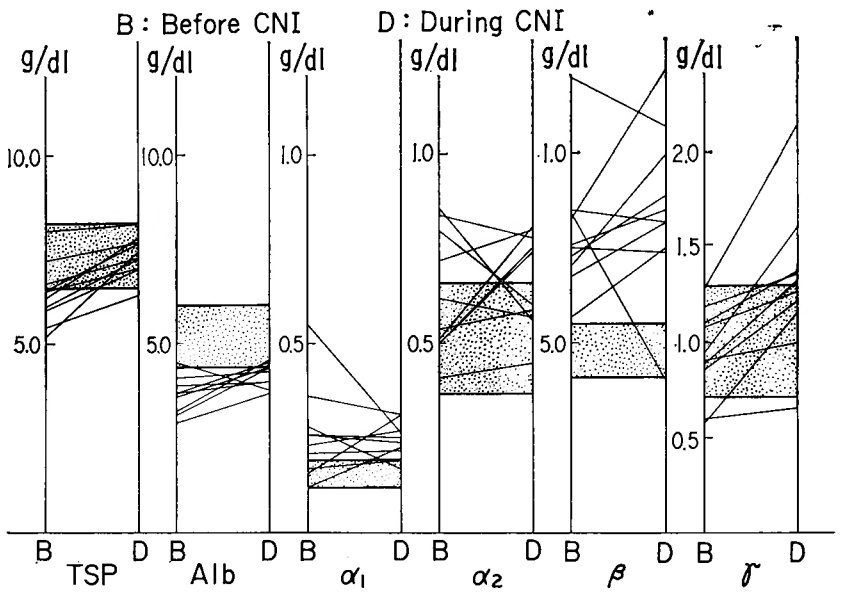

Fig. 9. changes in total serum protein, albumin, α_1-, α_2-, β-, and γ-globulin in ten patients before and during CNIc̄BCG.

a tendency to return to the normal range. Albumin also showed the same tendency as the total serum protein but it stayed below the normal minimum level in almost all the cases. α_1-Globulin increased in five but decreased in the rest. α_2-Globulin increased beyond the normal maximum level in three cases ; two of them died. β-Globulin increased in six but stayed, in general, above the normal maximum level in almost all the patients. γ-Globulin increased in all the cases. In half of them the normal maximum level was surpassed during CNI ; two of them died.

Changes in T-cells were followed before and during CNIc̄BCG in seven patients. Five of the seven showed a tendency for the T-cell count to increase after the commencement of CNI ; they are all doing well. The remaining two patients who showed a decrease in T-cells, died of recurrence of stomach cancer with wide-spread metastasis, as shown in Fig. 10. It is noteworthy that patients who showed an increase in T-cells after CNIc̄BCG survived longer than those whose T-cells decreased in the peripheral blood, suggesting that BCG has a stimulatory effect on proliferation of T-cells attacking target cancer cells.

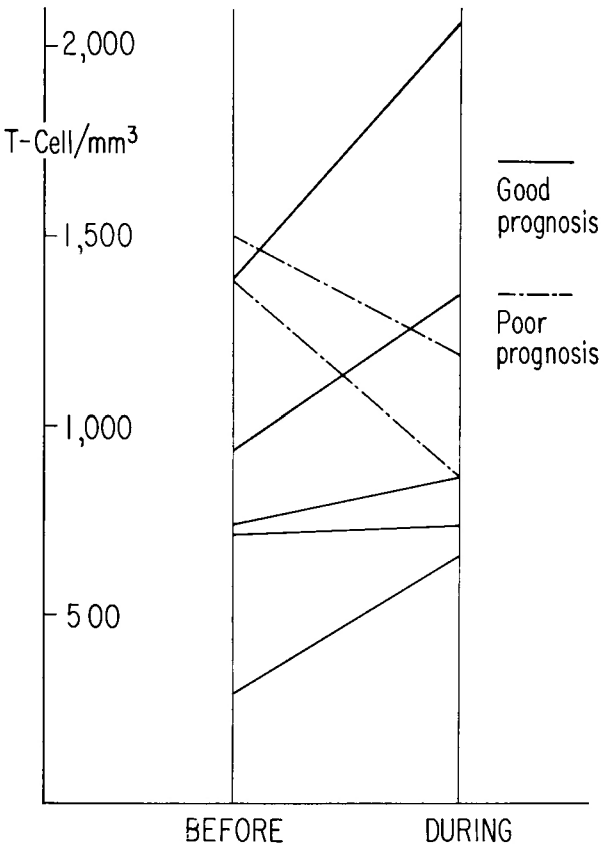

Fig. 10. changes in mean T-cell count per cubic millimeter of peripheral blood before and during CNIcBCG.

We would like to describe two representative cases from among the patients receiving CNIcBCG ; one died and the other has been cured of cancer. Changes in the main routine laboratory date of a 67-year-old female patient with advanced stomach cancer are shown in Fig. 11. The stage was IV. IgG showed a remarkable increase beyond the normal maximum level during CNI, while IgA and IgM stayed within the normal range. α_2- and γ-Globulin also increased after the start of CNI. T-cells decreased step by step during and after CNI. She eventually died of definite recurrence of cancer shortly after termination of the immunotherapy. It seems most likely that BCG hindered rather than helped the host cellular defense system through possible immunological enhancement in this case. Since this event we have made it a rule to discontinue CNIcBCG whenever such an untoward side effect is found. Fig. 12. shows changes of the main routine laboratory data of a 43-year-old male patient with stomach cancer of stage III. Three immunoglobulins stayed within their normal ranges throughout CNI. α_2- and γ-Globulin also stayed within the normal limits while the latter increased slightly after CNI. T-cells expressed

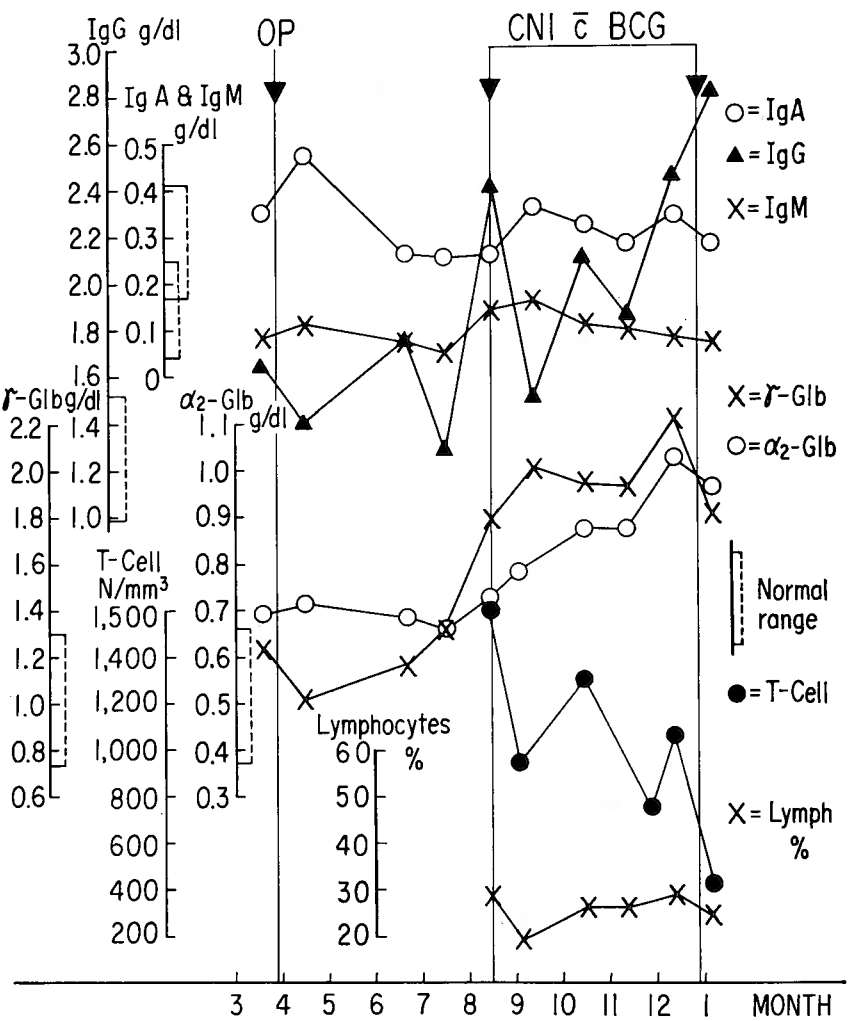

Fig. 11. changes of the main routine laboratory data in a 67-year-old female patient with advanced stomach cancer.

in number per cubic millimeters of the peripheral blood and the percentage of lymphocyces increased gradually during CNI. He is in good health without any sign of recurrence of cancer.

Comments

Since MORTON[2], and MATHÉ[1] reported the clinical effectiveness of immunotherapy with BCG in certain human malignant neoplasms, BCG immunotherapy has been evaluated for the treatment of common human malignant neoplasms throughout the world. Before discussing the clinical effectiveness of BCG immunotherapy, it should be emphasized that there are several important factors resulting in success or failure of BCG immunotherapy, as

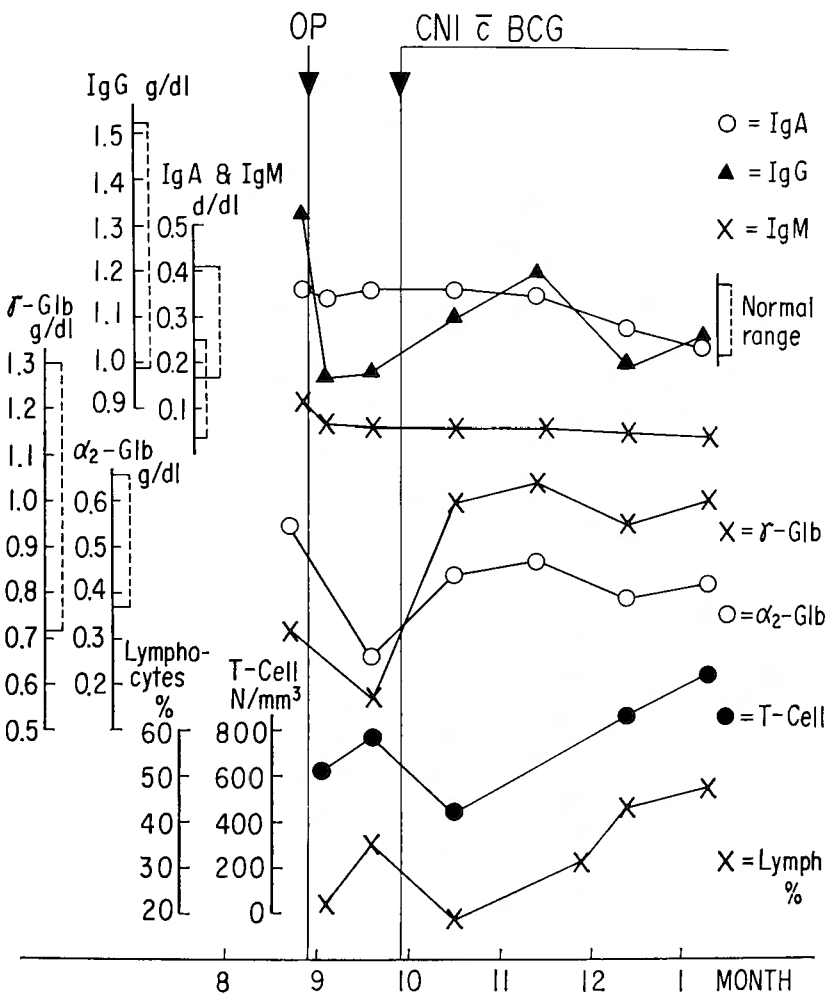

Fig. 12. changes of the main routine laboratory data in a 43-year-old male patient with stomach cancer of stage III.

BAST[6] et al. reported in their publications, such as tumor size, host immune response to BCG antigens, proximity between BCG site and tumor lesions, immunogenicity of the tumors, etc. In general, cancers of the gastrointestinal tract, such as stomach and colon, have been known to be weak in immunogenicity. Systemic administration of BCG in such cases may enhance rather than inhibit the growth of established tumors. It is essential, therefore, to remove the main tumor and metastatic lesions as completely as possible before the introduction of BCG immunotherapy. However, we have found that some patients in whom invasion of cancer cells was definitely found pathohistologically in the transected stump of the stomach are doing well without any signs of recurrence after receiving postoperative combination chemoimmunotherapy with CNIc̄BCG and FT 207. This combination chemoimmunotherapy appeared to be effective enough in patients with

far-advanced stomach cancers for them to return to work for three to six months although they eventually succumbed if they showed a positive reaction to BCG inoculation and their cancers were sensitive to FT 207. It is worth mentioning that a large proportion of patients with stomach cancers of various stages who showed a positive reaction to BCG survived longer than those with negative reaction. This finding is quite different from the results of tuberculin skin tests since more than half of the patients with stomach cancer had a negative reaction to tuberculin skin tests. The skin reaction to BCG appears to be more reliable than any other tests in determining the cellular immune response of patients with stomach cancers.

SIMMONS et al[5]. have tried to enhance the immunogenicity of certain experimental tumors by treating tumor cells with a hydrolytic enzyme, neuraminidase, and have reported the interesting result that they succeeded in conquering certain experimental tumors with BCG. We have treated some patients with stomach cancer by intradermal injections of a mixture of BCG and cancer cells in an attempt to induce a more specific immune response to their own cancers rather than a non-specific one. This was a trial aimed at enhancing the immunogenicity of stomach cancers. It was, however, discontinued because of the difficulty of obtaining pure cancer cell suspensions from excised cancerous tissues or meatastatic lymphnodes.

The main purpose of our CNIcBCG for patients with stomach cancer is to stimulate their cellular immune defence functions against cancers after the maximum reduction of the total number of cancer cells by any avilable means, such as surgery, chemotherapy, etc. We must warn you who are interested in CNIcBCG for postoperative patients with stomach cancer that CNIcBCG is not always the ideal supplemental cancer therapy. Care should be taken before, during, and after CNIcBCG. Whenever abnormal changes, such as abrupt increases in α_2- and γ-globulin, and IgG, a decrease in T-cell count and/or lymphocyte count, and decreases in blastoid transformation of lymphocytes and MIF, are detected after the commencement of CNIcBCG, it should be discontinued immediately. If you apply very carefully CNIcBCG to postoperative patients with stomach cancer by checking the above-mentioned changes in serum protein fractions and lymphocytes, CNIcBCG will be a promising supplemental cancer therapy.

Summary

The present study suggests that BCG immunotherapy may be effective as a supplemental cancer therapy for postoperative patients with stomach cancer. The true mechanism of CNIcBCG is not yet entirely understood. But it seems most likely that the effect of BCG is to control cancers by stimulating the host cellular immune defense system.

The delayed cutaneous hypersensitivity reaction to BCG appeared to be the most reliable skin test to judge the ability of patients to develop a cellular immune response. It should be emphasized that the indications for CNIcBCG use are limited to postoperative patients from whom the major tumor and metastatic lesions have been removed as completely

as possible. It should be discontinued immediately whenever untoward side effects are found during CNI-BCG.

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References

1) Mathé, G., Amiel, J. L., Schwarzenberg, L., et al. Active immunotherapy for acute lymphoblastic leukemia. Lancet, **1** : 697, 1969.
2) Morton, D.L., Eilber, F. R., Malmgren, R. A., et al. : Immunological factors which influence response to immunotherapy in malignant melanoma. Surgery, **68** : 158, 1970.
3) Old, L. J., Benacerraf, B., Clarke, D. A., et al. The role of the reticuloendothelial system in the host reaction to neoplasia. Cancer Res., **21** : 1281, 1961.
4) Sparks, F. C., Silverstein, M. J., Hunt, J. S., et al. : Complication of BCG immunotherapy in patients with cancer. N Engl J Med, **289** : 827, 1973.
5) Simmons, R. L., &Rios, A. : Immunospecific regression of methylcholanthrene fibrosarcoma using neuraminidase : III. Synergistic effect of BCG and neuraminidase treated tumor cells. Ann Surg, **176** : 188, 1972.
6) Bast, R. C. Jr., Zbar, B., et al. BCG and Cancer. N Engl J Med, **290** : 1413, 1974.

和文抄録

胃癌患者に対するBCG癌非特異的免疫療法

日本バプテスト病院　外科

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笠原　洋

1960年代後半よりBCGを使用した免疫療法が注目され，実際にMathéやMortonにより白血病，悪性黒色腫に対するBCGの臨床的有用性が報告された．我々は彼等の報告に着目し，消化器癌のうち特に胃癌に対しBCG癌非特異的免疫療法（CNIcBCG）を試みた．一般に胃癌は他の人癌に比較して，immunogenicityに乏しく，BCGは無効であるとされている．このような癌にBCGを異所的に全身的に投与することは，癌の増悪をおこす危険性が当然考えられなければならない．そこでまず外科手術により主要癌病巣および転移巣を可久的に除去したのちにBCG生菌の皮内接種をおこなったところ，従来の術後成績とことなり明らかに延命効果が認められた．切除断端に癌浸潤の認められた症例にも再発がおこりにくくなった．BCG皮内接種により生ずる反応が陽性の術後患者は陰性のものに比較し，予後が良好であることがわかった．ツベルクリン反応が陰性でも，BCGの反復接種により陽転する症例の予後は良好であった．CNIcBCGの本態はまだわかっていないが，担癌生体に宿主免疫防衛機能があるとすれば，BCGはこの機能を賦活する作用を有するものと推察される．しかし，CNIcBCGには副作用がある事を忘れてはいけない．即ち，液性抗体の増加に伴うblockiug factorの増大によるefferent or afferent immunological enhancementの危険性がひそんでいる事である．その他の副作用にも充分注意を払う必要がある．我々は免疫療法中は勿論その前後に定期的に血清免疫グロブリン，血清蛋白分画，肝機能，CRP，血液像特にT細胞，リンパ球百分率等の変動に細心の注意を払っている．若し免疫グログリン中のIgG，血清蛋白分画中のα_2-グロブリンとγ-グロブリンの異常増加，リンパ球百分率およびT細胞の減少，CRPの陽性化，GPT，アルカリフオスフアターゼの増加が同時に認められるときは，immunological enhancementがもっともうたがわれるため，ただちに免疫療法を中断することにしている．興味深い事は上述の異常変化が再発をおこして来た術後胃癌患者の殆んどすべてに認められたことである．そして異常は臨床症状が出現する1～2ヶ月前に検出可能である．この事は術後患者の予後の判定に役立つばかりでなく，他の適切な治療法をえらぶ余裕を与えてくれる．CNIcBCGはその適応を慎重に決定し，上述の諸検査を定時的に追跡しながらおこなえば，有望な補助的癌治療法であると思はれる．FT207との併用療法は特にすぐれたもので，実地医家におすすめ出来るものと思う．